Cutaneous Melanoma in Postmenopausal Women after Nonmelanoma Skin Carcinoma

The Women's Health Initiative Observational Study

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BACKGROUND. An elevated risk for cutaneous melanoma has been reported in individuals with nonmelanoma skin carcinoma (NMSC), but to the authors' knowledge, this association has not been prospectively studied in a large, multigeographic population of postmenopausal women.

METHODS. The association between NMSC and the incidence of cutaneous melanoma was assessed in the Women's Health Initiative Observational Study involving 67,030 non-Hispanic white postmenopausal women ages 50–79 years and who were free of prior other cancers at baseline. Cancer history, demographics, and previous and current risk exposures were determined by questionnaires at baseline and follow-up. Participants' reports of incident cutaneous melanoma collected annually were confirmed by physician review of medical records. Cox proportional hazards analyses were used to assess the relation of prior NMSC with incident cutaneous melanoma.

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RESULTS. In age-adjusted analysis, women with a history of NMSC but no other malignancy (n = 5552) were found to be 2.41 times more likely to develop cutaneous melanoma over a mean 6.5 years compared with women who had no history of NMSC (95% confidence interval [95% CI], 1.82–3.20). In a multivariate analysis, women with a history of NMSC and no other cancer history at baseline were 1.70 times more likely to develop cutaneous melanoma compared with women without NMSC (95% CI, 1.18–2.44).

CONCLUSION. The results of the current study provide evidence and further defines the magnitude of increased risk for cutaneous melanoma in postmenopausal non-Hispanic white women with a history of NMSC. ***Cancer*** **2006;106:654–63.**

KEYWORDS: melanoma, skin neoplasms, neoplasm-second primary, risk, postmenopause, female.

An increased risk for malignant melanoma has been reported in association with a history of basal or squamous cell carcinoma of the skin (i.e., nonmelanoma skin carcinoma [NMSC]) in men and women.[1–10] For example, death rates from melanoma in American men and women have been found to be 3.2–3.5 times higher in prospective mortality studies among those with NMSC compared with those without a history of NMSC.[11] Therefore, although NMSC by itself is a common and rarely fatal cancer that usually carries a clinically benign prognosis, it may portend the occurrence of the markedly less favorable malignancy of cutaneous melanoma.[12,13]

Evidence in women of an association between NMSC and melanoma was observed cross-sectionally in the large, multiethnic, multigeographic population of U.S. postmenopausal women in the Observational Study of the Women's Health Initiative (WHI).[14] In an age- and multivariate-adjusted analysis, women with a history of NMSC were 3.29 times (95% confidence interval [95% CI], 2.87–3.76) more likely to report having had cutaneous melanoma compared with women without a history of NMSC. However, this previous study was cross-sectional and could not establish a temporal correlation between NMSC and melanoma. Furthermore, the melanoma outcomes were self-reported and not confirmed by medical reports or records.

Previous studies investigating the occurrence of cutaneous melanoma in men and women with a history of NMSC have been limited by their small size, lack of a multigeographic cohort, absence of an NMSC-free comparison group, and an inability to address many important lifestyle and cancer risk factors and exposures (smoking, alcohol use, nutrition, sun exposure and skin type, latitude of residence, socioeconomic status, prior hormone therapy use, oral contraceptive use, family history, and medical surveillance), and other potentially confounding variables such as body mass index (BMI), physical activity, supplement use, and diabetes.[1–10,15]

In an effort to address limitations of the prior work, the current study was undertaken to prospectively ascertain the magnitude of risk for cutaneous melanoma occurrence in healthy postmenopausal women who report a history of NMSC, and to further examine and define factors that influence this association.

MATERIALS AND METHODS

Data were collected from the 93,676 community-dwelling, postmenopausal women enrolled between 1994 and 1998 in the WHI-Observational Study (WHI-OS) at 40 clinical centers distributed widely throughout the U.S. The overall study design of the WHI has been published previously.[16–18] Human subjects review committees at each participating institution, the coordinating center at the Fred Hutchinson Cancer Research Center, and the National Institutes of Health, reviewed and approved the study. Informed consent was obtained from all participants. The current analysis incorporates demographics and information regarding cancer history, smoking, diabetes, diet (food frequency questionnaire), supplement use, exercise, health care, prior hormone use, anthropometric measures, family history of cancer, and sunlight exposure derived from responses on self-completed and interview questionnaires, and from certified clinic staff measurement documentation at the first screening clinic visit.

Weight and height were measured using a calibrated balance beam scale and a wall-mounted stadiometer, respectively. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Physical activity was calculated as the estimated total energy expended per week per kilogram and assigned a metabolic equivalent (MET) value expressed as MET hours per week (MET-hrs/wk).[19] Data

regarding the effect of sunlight exposure on the skin and lifelong sun exposure history were collected from participant responses to questionnaires from the follow-up Year 4 questionnaires.

Geographic region was defined by location of the clinic that enrolled each participant. Clinics with a latitude $>$ 40° north, between 35° and 40° north, or $<$ 35° north were designated as falling in the northern, middle, or southern region, respectively.[14,20] Data regarding lifelong location of residence were not collected.

At the time of study entry, each woman reported whether she had ever been diagnosed with a cancer other than NMSC, and if so, what specific type(s) of cancer. A woman who reported any cancer other than NMSC was coded as having a history of cancer. Information regarding the history of NMSC was collected separately. Nonmissing values for these 2 variables were available for 77,233 non-Hispanic white women. Of these women, 10,203 reported a history of a malignancy other than NMSC and were excluded from the current analyses. Therefore, there were 67,030 WHI-OS participants (5552 with prior NMSC and 61,478 with no prior NMSC) included in the current analyses.

Women were mailed questionnaires annually to report any hospitalization and a wide variety of outcomes including cancers of any type. The average participant follow-up time was 6.54 years, with a maximum of 9.3 years as of February 29, 2004. Participants' reports of incident NMSC were recorded but were not confirmed by physician adjudication. Participants' reports of incident cutaneous malignant melanoma were confirmed by physician adjudicators after medical record review, including pathology reports, and coded as invasive, in situ, or borderline.[21]

Statistical Methods

The association between baseline descriptive characteristics and history of NMSC was examined using chi-squared tests. For all analyses, P-values $<$ 0.05 were considered to be statistically significant.

The time of an incident melanoma event was defined to be the number of days from study enrollment to the first postenrollment diagnosis of melanoma. The follow-up time was censored at the time of the last documented follow-up contact or death. Comparisons of incident melanoma by NMSC status at baseline were presented as age-adjusted hazard ratios (HRs) and 95% confidence intervals (95% CIs) from Cox proportional hazards analyses. The assumption of proportionality was tested by including an indicator for NMSC history and the product term between this indicator and follow-up time and using a likelihood ratio procedure to test for a zero coefficient for the product term. The assumption was satisfied. The primary outcome in these analyses was cutaneous malignant melanoma, with secondary analyses assessing invasive and in situ melanoma separately. There were four borderline melanomas and four with unknown tumor behavior that were not assessed separately given the small numbers, but were included in the analyses of the total overall melanoma outcome.

Time-dependent Cox modeling was used to examine the effect of NMSC history combined with incident NMSC on incident melanoma. Multivariate adjusted Cox proportional hazards models using complete case data were used to assess the effect of NMSC history after adjustment for multiple risk factors. Interactions between NMSC history and baseline risk factors were examined by adding a product term between NMSC history and the given characteristic to a model that included both variables as main effects. P-values for assessing statistical significance were computed from likelihood ratio tests comparing models with and without the interaction term. Thirty-one subgroup comparisons were tested; fewer than two tests would be expected to be significant by chance alone. These subgroups included age; BMI (kg/m^2); diabetes; smoking; alcohol use; current healthcare provider; prior hormone therapy use; prior oral contraceptive use; geographic region; effect of sunlight exposure on skin; summer and other season sun exposure during childhood, adolescence, and 30s; months per year doing yardwork; cups of regular coffee drank; physical activity; dietary intake of fat, calcium, and vitamins D, C, and E; supplement use; family history of cancer; and nonsteroidal antiinflammatory medication use. Women with missing data for a given risk factor were excluded from analyses incorporating that risk factor. All analyses were performed using the SAS System for Windows, version 9.1 (SAS Institute, Inc., Cary, NC).

RESULTS

Baseline descriptive characteristics including various known cancer risk factors are shown in Table 1 according to NMSC history. Women with a history of NMSC and no other cancer were more likely to be older, more highly educated, and in a higher income bracket than their non-NMSC counterparts. Furthermore, they were more likely to have a current healthcare provider, to have had a medical visit in the past year, to engage in routine physical activity, be of a lower BMI, have lower dietary fat intake, drink less regular coffee, and take dietary supplements. They were more likely to have smoked in the past, to drink one or more alcoholic beverages per week, and to have used hormone therapy. Women with NMSC were less likely to have used oral contraceptives and more likely

to have a family history of cancer, most notably breast cancer and ovarian cancer. Women with a history of NMSC were more likely to live in the southern or middle latitudes of the U.S. They had a greater propensity to burn rather than tan upon exposure to sunlight, as well as report greater summer sun exposure in their childhood and teen years than their non-NMSC counterparts.

Overall, non-Hispanic white women who reported that they had NMSC on enrollment were 2.41 times more likely to develop melanoma of the skin over a mean follow-up period of 6.5 years compared with women of the same age who had not had NMSC (95% CI, 1.82–3.20) (Table 2).

Women with a prior history of NMSC or incident NMSC diagnosed during the follow-up period were included in the assessment of subsequent melanoma incidence in Table 3. The incidence of melanoma in these women was found to be 2.54 times that of women without NMSC (95% CI, 1.94–3.33) after age adjustment. Subanalyses for both of these groups demonstrated that the HR for in situ melanoma was greater than that for invasive melanoma; however, the 95% CIs for both invasive and in situ melanoma overlap, making a difference in the correlation between prior NMSC and invasive versus in situ melanoma impossible to detect.

Factors potentially related to the development of cutaneous melanoma such as the effect of sunlight exposure on the skin, lifetime sun exposure habits, and a family history of cancer, were examined separately by NMSC history and adjusted for age in the 67,030 women (Table 4). Women without prior NMSC were significantly more likely to develop melanoma if they experienced a burn rather than a tanning effect from exposure to sunlight, and if they reported summer sun exposure of greater than 2 hours per day in their 30s. However, among those women with a history of NMSC, melanoma risk estimates were somewhat similar, but did not reach statistical significance with regard to sunlight's effect on the skin nor with regard to summer sun exposure in their 30s. This may be due in part to the smaller sample size available for women with a prior history of NMSC. Sun exposure in childhood and the teen years did not appear to impart a change in risk for the development of melanoma in either the non-NMSC or NMSC groups. Having a family history of ovarian cancer increased the risk for melanoma among women with NMSC, but not among non-NMSC women. Although the effects of some of these baseline risk factors on cutaneous melanoma were different when examined separately by NMSC status, results of interaction testing yielded no statistical evidence of a difference in the effect of these or any other baseline risk factors (31 risk factors total) on the association of NMSC with incidence of cutaneous melanoma (data not shown).

We further assessed the relation between a history of NMSC and the incidence of cutaneous melanoma using a multivariate analysis (Table 5). A woman with a history of NMSC and no history of any other cancer at baseline was 1.70 times (95% CI, 1.18–2.44) more likely to develop cutaneous melanoma after adjusting for age; socioeconomic level; education; smoking; alcohol use; cups per day of regular coffee; percentage of calories from fat; selenium and zinc intake from diet and supplements; history of diabetes; BMI; prior hormone therapy use; prior oral contraceptive use; current medical care provider; geographic region by latitude; sun exposure in childhood, adolescence, and 30s; and family history of any cancer. Similar to the age-adjusted model, the HRs and 95% CIs for invasive versus in situ melanoma overlap; therefore, no difference was detected with regard to the correlation between prior NMSC and invasive versus in situ melanoma in the multivariate-adjusted model.

DISCUSSION

This prospective study, which was undertaken in a large and clinically well-characterized sample of U.S. women, supports and further defines the magnitude of increased risk for cutaneous melanoma in non-Hispanic white postmenopausal women ages 50–79 years with a history of NMSC compared with those without NMSC. An increased risk for cutaneous melanoma was found in all age groups studied (ages 50–79 yrs), in women living in different latitudes of the U.S., for those with varying levels of lifelong sun exposure history and skin reactions to the sun, in those with both high and low BMI, in women who had used hormone therapy or taken dietary supplements and those who did not, in smokers and in never smokers, and in women with or without a family history of any cancer.

Previous studies of the subsequent occurrence of cutaneous melanoma after NMSC in U.S. women were unable to specifically address important potential confounding factors such as lifestyle variables, medical surveillance bias, sun exposure history, and nutrient intake, which may account for some or all of the association.[1–10] In the current study, extensive data were available from the WHI-OS, including prior hormone therapy and oral contraceptive use, percent of dietary calories from fat, dietary supplement usage, level of physical activity, geographic region, sun exposure history, smoking and alcohol status, education, socioeconomic level, diabetes, and access to medical care.

TABLE 1
Baseline Characteristics of Non-Hispanic White WHI-OS Participants with and without NMSC History

	NMSC ever				Total		
	No (n = 61,478)		Yes (n = 5552)		(n = 67,030)		
	No.	%	No.	%	No.	%	P value[a]
Age at screening in yrs							< 0.001
50–59	19,793	32.2	1207	21.7	21,000	31.3	
60–69	27,301	44.4	2574	46.4	29,875	44.6	
70–79	14,384	23.4	1771	31.9	16,155	24.1	
Education							< 0.001
None-high school diploma/GED	12,375	20.3	794	14.4	13,169	19.8	
School after high school	22,324	36.6	1906	34.5	24,230	36.4	
College degree or higher	26,328	43.1	2817	51.1	29,145	43.8	
Family income							< 0.001
< $10,000	1658	2.9	125	2.4	1783	2.9	
$10,000–$19,999	5968	10.4	468	9.1	6436	10.3	
$20,000–$34,999	13,286	23.2	1150	22.4	14,436	23.2	
$35,000–$49,999	11,728	20.5	1092	21.3	12,820	20.6	
$50,000–$74,999	12,016	21.0	1063	20.7	13,079	21.0	
≥$75,000 +	12,538	21.9	1240	24.1	13,778	22.1	
BMI in kg/m^2							< 0.001
< 25	25,913	42.6	2638	48.0	28,551	43.1	
25–29	20,744	34.1	1826	33.2	22,570	34.1	
≥ 30	14,112	23.2	1030	18.7	15,142	22.9	
Smoking							0.12
Never	30,387	50.0	2699	49.1	33,086	49.9	
Past	26,787	44.1	2499	45.4	29,286	44.2	
Current	3570	5.9	302	5.5	3872	5.8	
Alcohol use							< 0.001
< 1 drink per week	35,537	58.1	3026	54.7	38,563	57.8	
1 to > 7 drinks per week	17,106	27.9	1634	29.5	18,740	28.1	
≥ 7drinks per week	8560	14.0	870	15.7	9430	14.1	
Cups of regular coffee/day							< 0.001
None	25,596	42.0	2518	45.7	28,114	42.3	
1	9173	15.1	869	15.8	10,042	15.1	
2–3	19,345	31.7	1620	29.4	20,965	31.6	
4–5	5372	8.8	408	7.4	5780	8.7	
≥ 6	1458	2.4	89	1.6	1547	2.3	
Current health care provider	58,165	95.4	5295	96.3	63,460	95.4	0.001
Medical visit within the last year	49,930	83.6	4611	85.6	54,541	83.8	< 0.001
Diabetes	2592	4.2	239	4.3	2831	4.2	0.76
Prior hormone therapy use							< 0.001
None	23,087	37.6	1924	34.7	25,011	37.3	
Estrogen alone only	18,885	30.7	1818	32.7	20,703	30.9	
Estrogen plus progesterone only	15,417	25.1	1370	24.7	16,787	25.0	
Both	4089	6.7	440	7.9	4529	6.8	
Prior oral contraceptive use in yrs							0.001
Nonuser	35,809	58.3	3361	60.5	39,170	58.5	
< 5	14,371	23.4	1169	21.1	15,540	23.2	
5–10	5688	9.3	495	8.9	6183	9.2	
≥ 10	5592	9.1	527	9.5	6119	9.1	
Geographic region by latitude							< 0.001
Southern: < 35 degrees North	16,774	27.3	1978	35.6	18,752	28.0	
Middle: 35–40 degrees North	17,115	27.8	1614	29.1	18,729	27.9	
Northern: > 40 degrees North	27,589	44.9	1960	35.3	29,549	44.1	
Effect of sunlight exposure on skin							< 0.001
No change in skin color	3279	6.0	297	6.0	3576	6.0	
Tans but does not burn	16,732	30.8	1020	20.7	17,752	30.0	
Burns, then tans	13,957	25.7	1154	23.5	15,111	25.5	
Burns, then tans a minimal amount	14,458	26.6	1564	31.8	16,022	27.1	
Burns but does not tan	5877	10.8	881	17.9	6758	11.4	

(continued)

TABLE 1
(Continued)

	NMSC ever				Total		
	No (n = 61,478)		Yes (n = 5552)		(n = 67,030)		
	No.	%	No.	%	No.	%	P value[a]
Childhood summer sun exposure in hrs/day > 2	39,333	71.4	3674	72.8	43,007	71.5	0.04
Teen summer sun exposure in hrs/day > 2	33,111	60.2	3147	62.4	36,258	60.3	0.002
30s summer sun exposure in hrs/day > 2	17,538	31.8	1654	32.9	19,192	31.9	0.14
Mos/yr in the yard							< 0.001
< 1	24,113	39.5	2197	39.9	26,310	39.5	
1–3	10,693	17.5	896	16.3	11,589	17.4	
4–6	11,751	19.3	981	17.8	12,732	19.1	
7–9	7080	11.6	658	11.9	7738	11.6	
10–12	7395	12.1	780	14.2	8175	12.3	
Physical activity in MET, hrs/week							<0.001
None	7677	12.7	576	10.6	8253	12.6	
> 0–7.4	16,414	27.3	1387	25.5	17,801	27.1	
7.5–17.4	18,015	29.9	1700	31.2	19,715	30.0	
≥ 17.5	18,124	30.1	1779	32.7	19,903	30.3	
Percent of total calories from fat							< 0.001
≤ 30	28,472	47.7	2737	50.5	31,209	47.9	
> 30–35	12,485	20.9	1142	21.1	13,627	20.9	
> 35–40	9380	15.7	825	15.2	10,205	15.7	
> 40	9380	15.7	721	13.3	10,101	15.5	
Dietary selenium in μg							0.09
≤ 71.3	19,037	31.9	1664	30.7	20,701	31.8	
71.4–101.6	20,578	34.5	1940	35.8	22,518	34.6	
> 101.6	20,102	33.7	1821	33.6	21,923	33.7	
Dietary zinc in mg							< 0.001
≤ 7.9	18,519	31.0	1521	28.0	20,040	30.8	
8.0–11.6	20,490	34.3	1959	36.1	22,449	34.5	
> 11.6	20,708	34.7	1945	35.9	22,653	34.8	
Supplement use (any)	45,854	74.6	4415	79.5	50,269	75.0	< 0.001
Selenium	24,772	40.3	2397	43.2	27,169	40.5	< 0.001
Zinc	28,634	46.6	2826	50.9	31,460	46.9	< 0.001
Family history of any cancer	39,780	67.2	3865	72.2	43,645	67.6	< 0.001
Breast cancer	11,274	19.3	1146	21.8	12,420	19.5	< 0.001
Ovarian cancer	622	1.3	69	1.6	691	1.3	0.10

WHI-OS: Women's Health Initiative–Observational Study; NMSC: nonmelanoma skin cancer; GED: general equivalency diploma; BMI: body mass index; E: estrogen; P: progesterone.MET: metabolic equivalent.
[a] P values were derived from chi-square tests.

Because sunlight is considered the main environmental cause of both NMSC and cutaneous melanoma, and given the strong relationship in the U.S. of southern latitude residence and NMSC history, it is important to control for geographic latitude of residence and history of lifetime sun exposure.[12,13,20,22–24] After adjusting for these confounding factors as well as others, the HR for the association between NMSC and melanoma development is reduced to 1.70. A change of this magnitude suggests that several of the covariates are related to both exposure and outcome.

Controlling for medical surveillance appears to be especially important given the univariate relation of current healthcare provider with NMSC (Table 1), and the possibility that those who had NMSC would be more likely to undergo skin inspection by a physician on a regular basis, and therefore be diagnosed with cutaneous melanoma more readily. Although we did adjust for having a medical provider, our medical surveillance adjustment is limited due to a lack of information on the frequency or quality of skin examinations specifically. Furthermore, although invasive and in situ melanomas were diagnosed with similar frequency, we did not have pathologic information available for Breslow thickness; therefore, surveillance bias could not be eliminated based on pathologic diagnosis.[25]

The current study relied entirely on self-report of

TABLE 2
Incidence (Annualized %) of Cutaneous Melanoma in Non-Hispanic White WHI-OS Participants for Participants with and without NMSC History

	History of NMSC						
	No		Yes				
	No.	%	No.	%	Adjusted HR	95% CI	*P* value
Number enrolled	61,478		5552				
Mean follow-up in yrs (SD)	6.5 (1.4)		6.5 (1.4)				
Melanoma of the skin	272	(0.07)	59	(0.16)	2.41	1.82–3.20	< 0.0001
Invasive	153	(0.04)	29	(0.08)	2.15	1.44–3.21	0.0002
In situ	113	(0.03)	28	(0.08)	2.66	1.75–4.03	< 0.0001

WHI-OS: Women's Health Initiative–Observational Study; NMSC: nonmelanoma skin cancer; HR: hazards ratio; 95% CI: 95% confidence interval; SD: standard deviation.
The hazard ratios, 95% confidence intervals, and *P* values were derived from Cox proportional hazards analyses and were adjusted for age.

TABLE 3
Cutaneous Melanoma HRs for Non-Hispanic White WHI-OS Participants with a History of NMSC at Baseline or NMSC Prior to Melanoma during Follow-Up[a]

	Prior NMSC				
	No	Yes	Adjusted HR	95% CI	*P* value
Melanoma of the skin	265	66	2.54	1.94–3.33	< 0.0001
Invasive	150	32	2.22	1.51–3.25	< 0.0001
In situ	110	31	2.78	1.86–4.15	< 0.0001

HR: hazards ratio; WHI-OS: Women's Health Initiative–Observational Study; NMSC: nonmelanoma skin cancer; 95% CI: 95% confidence interval.
[a] Prior nonmelanoma skin cancer (NMSC) includes a history of NMSC at baseline or incident NMSC occurring during follow-up prior to cutaneous melanoma. Hazard ratios, 95% confidence intervals, and *P* values were from Cox proportional hazards analyses and were adjusted for age.

NMSC overall, and could not differentiate whether a particular histologic subtype (i.e., squamous cell vs. basal cell) was differentially associated with melanoma. Furthermore, the validity of self-reported NMSC within the WHI-OS has not been assessed to our knowledge. However, recent studies suggest that self-reported NMSC has a high degree of accuracy.[26] For example, Ming et al.[26] found that patients correctly identified their overall NMSC status in 91.8% of cases, and Colditz et al.[27] reported from the Nurses Health Study that > 90% of self-reported cases of cancer of the skin were confirmed by histopathology reports. Therefore, although the current study relied only on self-report of NMSC, prior research strongly supports a high rate of agreement with actual diagnosis of NMSC.

The current study was limited to observations in postmenopausal non-Hispanic white women ages 50–79 years only, and furthermore excluded women with a prior history of any cancer other than NMSC. Therefore, the magnitude of the association may be underestimated. Further assessment of the extent of the association for women age < 50 years, those of non-white and Hispanic ethnicities, premenopausal women, and men is warranted.

Epidemiologic findings support an association between fair skin, inability to tan, and the risk of both melanoma and NMSC.[12,22,28,29] For whites in the U.S., the incidence of NMSC is associated with age and lifelong residence in areas with high levels of ambient ultraviolet B (UVB) radiation (i.e., lower latitude).[12,13,22,30,31] Although chronic, cumulative, UV exposure appears to be the most important risk factor for developing NMSC overall, recent studies suggest that intermittent intense sun exposure early in life, leading to sunburn, may also be a risk factor for some basal cell carcinomas.[23,30,32] Cutaneous melanoma is believed to be associated with intense intermittent sun exposure and sunburn. Yet the optimal relation between melanoma risk and the dose of sun exposure received is complex and appears to vary according to age, the dose received, and host characteristics.[23,33,34] In the current study, women without a history of NMSC, but not those with such a history, were more likely to develop melanoma if they reported experiencing a burn rather than a tanning effect from exposure to sunlight and if they reported summer sun exposure greater than 2 hours per day in their 30s (Table 4). These findings support the concept that distinct, dual, gene-environment interactive pathways lead to cutaneous melanoma in NMSC and non-NMSC women.[23,35] For example, researchers have found that BRAF mutations were more common in melanomas occurring on intermittently sun-exposed skin than on chronically sun-damaged skin.[36] There may be a molecular distinction between those individuals whose melanomas arise on chronic sun-ex-

TABLE 4
Association of Various Risk Factors with Cutaneous Melanoma by History of NMSC[a]

	History of NMSC					
	No (n = 61,478)			Yes (n = 5552)		
	HR	95% CI	P value	HR	95% CI	P value
Effect of sunlight exposure on skin						
Tans but does not burn	1.00			1.00		
No change in skin color	0.71	0.32–1.58	0.40	1.18	0.24–5.88	0.84
Burns, then tans	1.51	1.04–2.20	0.03	1.80	0.67–4.83	0.24
Burns, then tans a minimal amount	2.04	1.44–2.89	< 0.01	2.33	0.94–5.79	0.07
Burns but does not tan	2.25	1.48–3.42	< 0.01	1.96	0.71–5.40	0.19
30 summer sun exposure > 2 hrs/day	1.48	1.15–1.91	< 0.01	1.19	0.68–2.09	0.54
Family history of ovarian cancer	0.72	0.18–2.89	0.64	4.26	1.32–13.75	0.02

NMSC: nonmelanoma skin cancer; HR: hazards ratio; 95% CI: 95% confidence interval.
[a] Cox proportional hazards models examined the effect of each risk factor separately and were adjusted for age.

TABLE 5
Incidence (Annualized %) of Cutaneous Melanoma and Multivariate-Adjusted[a] HRs in Non-Hispanic White WHI-OS Participants for a History of NMSC

	History of NMSC						
	No		Yes		HR	95% CI	P value
Melanoma	203	(0.07%)	36	(0.14%)	1.70	1.18–2.44	0.004
Invasive	112	(0.04%)	20	(0.08%)	1.69	1.04–2.75	0.03
In situ	86	(0.03%)	15	(0.06%)	1.69	0.96–2.95	0.07

HR: hazards ratio; WHI-OS: Women's Health Initiative–Observational Study; NMSC: nonmelanoma skin cancer; 95% CI: 95% confidence interval.
[a] Cox proportional hazards models were adjusted for age; education; socioeconomic level (income); smoking; alcohol use; cups per day of regular coffee; percent calories from fat; selenium and zinc intake from diet and supplements; history of diabetes; body mass index (kg/m^2); prior hormone therapy use; prior oral contraceptive use; current medical care provider; geographic region by latitude; sun exposure in childhood, adolescence, and 30s; and family history of cancer.

posed skin such as in many of those with NMSC, and those in whom melanoma develops on sun-protected, fair, or non-NMSC skin.

Previous investigations report findings in both animal and human models of common etiologic mechanisms for both NMSC and cutaneous melanoma that support the association observed in the current study. A qualitative impairment of the immune response, exemplified by the elevated production of type 2 cytokines, and the concomitant reduction in type 1 cytokines, have been reported in basal and squamous cell skin carcinomas and melanoma.[12,37–41] A number of oncogenes and suppressor genes have been implicated in the genesis and progression of both NMSC and cutaneous melanoma. UV-induced reduction of DNA repair capacity, as well as early- and late-stage p53 suppressor gene mutations, have been documented to play a role in NMSC and cutaneous melanoma.[42–50] Still another example of common etiologies regards the BRCA2 gene, which encodes a protein important in DNA repair. BRCA2 mutation carriers have an increased risk of breast and ovarian cancer, as well as melanoma.[51] Interestingly, in the current study, women in the NMSC group were more likely to have a family history of breast or ovarian cancer compared with their non-NMSC counterparts. Furthermore, among women with NMSC a family history of ovarian cancer increased the risk for melanoma, whereas this was not observed among women in the non-NMSC group. These characteristics and findings in the women with NMSC may suggest that a BRCA2 gene is involved in the association of NMSC and melanoma.

Consequently, in NMSC and non-NMSC populations of women, different predisposing genes may interact with sun exposure and cause defective molecular signaling, and therefore influence the probability of melanoma development. If multiple molecular pathways to melanoma development are supported by other investigations, public health messages can be tailored to the population at risk.[52]

It is estimated that over 1.3 million cases of NMSC are diagnosed yearly in the U.S., making it the most common (yet largely undocumented) cancer entity in the U.S.[53,54] NMSCs are not routinely included in U.S. cancer registries. Furthermore, because NMSC usually carries a favorable prognosis, patients are unlikely to be questioned specifically regarding a history of NMSC during the course of a routine general physical examination. These factors hamper the ability to calculate the incidence and prevalence of NMSC accurately, as well as monitor trends and associations.

Cutaneous melanoma (invasive) was estimated to affect 59,580 Americans in 2005 (26,000 women), and account for 7770 deaths (2860 women). An additional 46,170 individuals will be affected with cutaneous melanoma in situ.[29,55] Noted for its rapid rise in incidence, its high mortality rate in patients with advanced disease, and as a leading cause of lost productive years, melanoma is routinely included in U.S. cancer registries.[29,53,56,57] Nevertheless, much of the registries' information does not include epidemiologic risk information, including documentation of NMSC. Efforts to reduce the incidence of cutaneous melanoma in individuals age $>$ 50 years are focused on secondary, rather than primary prevention (i.e., screening persons at high risk).[29,57,58] In the WHI-OS, 8% of the women enrolled reported a history of NMSC.[14] In the current study, the annual incidence of melanoma in non-Hispanic white women with a history of NMSC was 160/100,000 versus 70/100,000 for women without a history of NMSC. The high prevalence of NMSC in non-Hispanic white postmenopausal women in the U.S., and its link to an increased risk of subsequent cutaneous melanoma as delineated in this study, is important not only for further defining melanoma risk in white postmenopausal women, but also for sensitizing the medical community to this risk and for developing new routines of follow-up and patient assessment by medical providers to promote the early detection of melanoma.

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